PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
502008/MRO/ged		
International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU2003/001676	16 December 2003	16 December 2002

International Patent Classification (IPC) or national classification and IPC

Int. Cl.[7] C12N 15/00, C12Q 1/25, A01K 67/00

Applicant

GARVAN INSTITUTE OF MEDICAL RESEARCH et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of the report
2 June 2004	6 April 2005
Name and mailing address of the IPEA/AU	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001676

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed.

[ ] the description, pages , as originally filed,
pages , filed with the demand;
pages , received on with the letter of

[ ] the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[ ] the drawings, pages , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[X] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-94, 99-101	YES
	Claims	95-98	NO
Inventive step (IS)	Claims	1-94	YES
	Claims	95-101	NO
Industrial applicability (IA)	Claims	1-101	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Citations.

D1 Khan AH, Pessin JE. Insulin regulation of glucose uptake: a complex interplay of intracellular signalling pathways. Diabetologia. 2002 Nov. 45(11): 1475-83. 2002 Oct 18. Review.

D2 Liu Jun; Kimura Akiko; Baumann Christian A; Saltiel Alan R. APS facilitates c-Cbl tyrosine phosphorylation and GLUT4 translocation in response to insulin in 3T3-L1 adipocytes. Molecular and Cellular Biology, (2002 Jun). 22 (11) 3599-609.

D3 Yokoi Norihide; Komeda Kajuro; Wang He-Yao; Yano Hideki; Kitada Kazuhiro; Saitoh Yuka; Seino Yutaka; Yasuda Kazuki; Serikawa Tadao; Seino Susumu. Cblb is a major susceptibility gene for rat type 1 diabetes mellitus. Nature Genetics, (2002 Aug) 31 (4) 391-4.

D4 Chiang SH, Baumann CA, Kanzaki M, Thurmond DC, Watson RT, Neudauer CL, Macara IG, Pessin JE, Saltiel AR. Insulin-stimulated GLUT4 translocation requires the CAP-dependent activation of TC10. Nature, 2001 Apr 19; 410(6831): 944-8.

D5 Ahmed Z, Smith BJ, Pillay TS. The APS adapter protein couples the insulin receptor to the phosphorylation of c-Cbl and facilitates ligand-stimulated ubiquitination of the insulin receptor. FEBS Lett. 2000 Jun 9; 475(1): 31-4.

D5 Baumann CA, Ribon V, Kanzaki M, Thurmond DC, Mora S, Shigematsu S, Bickel PE, Pessin JE, Saltiel AR. CAP defines a second signalling pathway required for insulin-stimulated glucose transport. Nature. 2000 Sep 14; 407(6801): 202-7.

Novelty.

None of the prior art discloses that a genetically modified animal deficient in Cbl expression would have use in assays to determine compounds that modulate feeding behaviour, fat deposition, metabolic rate, or muscle/fat ratios. Nor does the prior art disclose the siRNA or shRNA molecules of SEQ ID NOs 4-239. Thus claims 1-94, 99-101 are novel.

Claims 95-98 are to methods of producing compounds identified by the assays of claims 1-94. However, the method whereby a compound is identified is irrelevant to any method for its production. Insofar as the claims encompass known methods for producing known compounds, they are *prima facie* not novel.

Continued in Supplemental Box V

Supplemental Box V
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Novelty and Inventive Step

Inventive Step.

The problem of the invention is to find pharmaceutical compounds useful in the prophylaxis or treatment of NIDDM, ie that show effects on processes associated with insulin mediated glucose uptake.

The present invention is based on the applicants' discovery that $Cbl^{-/-}$ animals exhibit enhanced metabolic rates, increased muscle to fat ratios caused by altered fat deposition rates, increased appetite, and smaller adipocytes.

While the prior art discloses the role of Cbl in insulin mediated glucose uptake, it is not considered that it would be obvious that disruption of Cbl would necessarily produce the phenotypic results disclosed by the applicants. Therefore it cannot be considered obvious to use $Cbl^{-/-}$ animals, or known properties of the Cbl protein, or phosphorylation of the Cbl protein to assay for compounds that modulate feeding behaviour, fat deposition, metabolic rate or the ratio of lean muscle to body fat in a subject.

Thus claims 1-94 are accepted as inventive.

Claims 95-98 are to methods of producing compounds identified by the assays of claims 1-94. However, the method whereby a compound is identified is irrelevant to any method for its production. Thus, in so far as the claims are to methods for producing known classes of compounds, eg antibodies or antisense oligonucleotides or RNA interference molecules, to known genes or proteins, they cannot be accepted as inventive.

Claims 99-101 are to the use of RNA interference molecules derived from the sequence of a Cbl gene to modulate expression of Cbl. The production of RNA interference molecules and testing to determine their efficacy in modulating gene expression is a routine method of the art. Cbl genes are known, and the protein is known to ubiquinate receptors (see p4, lines 4-15). Its connection with insulin mediated glucose uptake is also known. Thus one skilled in the art would readily predict that modulation of Cbl by RNA interference would have measurable effects on some metabolism associated phenotypes of a cell, tissue or living animal; would inhibit or decrease the level of Cbl protein; and would inhibit or decrease Cbl-mediated ubiquination.

Therefore, claims 95-101 are not inventive.